2. RESPONSE/REMARKS

2.1 STATUS OF THE CLAIMS

Claims 1-20 were pending at the time of the Action.

Claims 3-5 have been withdrawn from consideration as non-elected species.

Claims 6-9 have been canceled herein without prejudice or disclaimer.

Claims 1, 13, 14, 17, 18 and 20 have been amended herein.

Claims 21-23 have been added herein.

Claims 1-5 and 10-23 remain pending in the case.

Upon allowance of claims to the elected species, Applicants give constructive notice of their intention to seek rejoinder of the non-elected species, including those specifically recited in currently-withdrawn claims 3 to 5.

2.2 SUPPORT FOR THE CLAIMS

Support for the pending claims can be found throughout the original claims, specification and figures as filed. It will be understood that no new matter is included within any of the present claims. In light of the claims canceled to date, Applicants believe no fees are due for the entry of new claims 21-23 (based upon the original specification and original claims 1, 6-9, 14-14 and 17); however, should any fee be necessary in connection with entry of the present amendment, the Commissioner is authorized to deduct such fees from the deposit account referenced *supra*.

2.3 THE OBJECTION TO CLAIM 14 IS OVERCOME.

Claim 14 was objected to because of informalities. The Examiner has requested Applicants amend claim 14 (and, presumably for the same reason, claim 13) to refer to the actual chemical structures of the recited compounds.

Responsive to this request, Applicants have amended claims 13 and 14 to recite the specific chemical structures of the enumerated compounds. Applicants have also amended the specification on pages 5 and 12 to provide the chemical structures of the recited compounds.

The amendment is proper, as the specification at page 1 line 11 explicitly incorporated by reference all of the documents cited in the application. Among those, the specification at page 2, line 14 explicitly recited incorporation of PCT Intl. Pat. Appl. No. AU02/01427, the application recited in original claims 13 and 14. Recitation of this copending PCT international application (which later gave rise to Section 371 United States Appl. No. 10/493,117 [published 9/28/06 as 20060217530]) is also specifically found in the original specification at least on page 5 at lines 18-22, and again on page 12 at lines 4 to 10. Therefore, entry of the amendment is proper, and no new matter is incorporated.

2.4 THE REJECTION UNDER 35 U. S. C. § 112 (2ND PARAGRAPH) IS OVERCOME.

Claim 20 was rejected, allegedly because the term "at least the step" as indefinite. The Examiner states that it "is not clear whether the treatment method comprises an additional step not recited in the claim," and the Action further notes "(i)t is not clear if the "ate least the step" is intended to limit the treatment method and what relationship is intended between the preamble and the additional method step."

Applicants respectfully traverse.

Use of the "comprising" transitional in this claim *clearly and unambiguously* sets forth the limitation that the claimed method encompasses not only the single recited step of administering to a subject in need thereof an effective amount of a pharmaceutically-acceptable composition that comprises a C5a G protein-coupled receptor inhibitor, but may also optionally comprise one or more additional steps other than the recited step of administering.

For example, the method of providing the composition to a subject in need thereof, may also further include one or more optional steps routinely found in the pharmaceutical arts—for example, the method may further optionally comprise a step of *rehydrating* the compound with a suitable diluent prior to administering the compound; or the method may further optionally comprise a step of *diluting* the compound to an appropriate dosage prior to administration. Similarly, the claimed method may also further optionally comprise an additional optional step of providing the compound to the subject in one or more doses *subsequent* to the initial administration step.

The phrase "at least the step of" is also equally clear and unambiguous. Simply stated, the claimed method includes at least the *recited* step of administering, but may also, optionally, comprise one or more *additional* steps in the performance of the method. Because of the wide use of the phrase in U.S. patent law, because of its plain language" meaning, and further because of the clear, unambiguous recitation of the phrase with the "comprising" transitional, Applicants respectfully assert that the term is fully definite and precise.

However, Applicants are also mindful of patent term considerations, economic factors, commercial relevance, and potential costs associated with a protracted examination. Therefore, (and solely in order to advance certain claims of particular scope to rapid allowance in view of commercialization and other market-based influences) without acquiescing in any way to the

propriety of the present rejection, Applicants have provided the present amendment to particularly point out and to even more precisely claim that which they regard as their invention. Applicants believe this clarification completely addresses the concern raised by the Examiner, and now respectfully request that the rejection be withdrawn.

2.5 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 112 (1ST PARAGRAPH) IS OVERCOME

Claims 1-2 and 6-20 were rejected allegedly as failing to comply with the written description requirement. The claims allegedly "contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants respectfully traverse.

However, Applicants are also mindful of patent term considerations, economic factors, commercial relevance, and potential costs associated with a protracted examination. Therefore, (and solely in order to advance certain claims of particular scope to rapid allowance in view of commercialization and other market-based influences) without acquiescing in any way to the propriety of the present scope rejection, Applicants have provided the present amendment to particularly address certain aspects of concern raised by the Examiner, and to facilitate a ready allowance of the pending claims. Applicants believe that the Specification is fully enabling for methods of treating osteoarthritis (OA) that comprise at least the step of providing to a subject in need of such treatment an effective amount of a C5a G protein-coupled receptor antagonist that is a cyclic peptide or peptidomimetic compound of general formula I, that is essentially devoid of agonist activity. Applicants further believe that the Specification contains the requisite written description (as evidenced by the exhaustive listing of C5a antagonist compounds, and also the

presence of significant *in vivo* experimentation in a suitable animal model of disease) to demonstrate not only that the Applicants were in possession of the invention at the time the application was filed, but that the specification as filed is not lacking for sufficient written description or the required enablement (see *infra*).

However, in the interest of expediting the closure of prosecution on the merits in the present application, and with an interest of proceeding claims of particular commercial relevance to allowance and issuance, Applicants have amended claims 1, 13, and 17 to more particularly point out, and to further distinctly claim particular C5a G protein-coupled receptor antagonists, which lack substantial agonist activity, and are useful in the treatment of OA in afflicted subjects.

Applicants believe that claims directed to the use of cyclic peptides and/or cyclic peptidomimetic compounds of general formula I, are all fully supported by the present Specification, and are free from rejection under this section of the Statutes. To that end, Applicants respectfully request that the present rejection be withdrawn.

2.6 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 112 (1ST PARAGRAPH) IS OVERCOME

Claims 1-2 and 6-20 were rejected allegedly as failing to comply with the enablement requirement. The Action states that while the specification is "enabling for methods to treat osteoarthritis mediated via the C5a receptor utilizing a C5a receptor antagonist," it allegedly does not provide sufficient enablement to treat the disease using any non-C5a receptor antagonists.

Applicants respectfully traverse.

It is well established that it is not Applicants' burden to defend their disclosure in the first instance: "(a)s a matter of patent office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless there is reason to doubt the objective truth of the statements contained therein* which must be relied on for enabling support."

The fact that the Action admits on page 10 that the specification provides detailed working examples that demonstrate efficacy of the claimed C5a G protein-couple antagonist compounds when used in a dog model of OA, the Action nevertheless appears to reject the pending method claims due to an alleged lack of nexus between the examples provided in the form of both *in vitro* activity and *in vivo* animal model data and the "ultimate" use of the various methods as a therapeutic regimen for the treatment of humans.

Applicants believe this rejection is misplaced. First, there is no requirement under the law that the Specification need enable *all* practical uses of the disclosed methods, nor does the Specification need to enable the claimed methods for each and every species of compounds recited in the genus. In fact, the standard for determining whether a *prima facie* case exists is to question whether or not the Specification enables a *credible and substantial utility* for the claimed invention.

All that is required to enable the claimed invention is an objective teaching concerning the use of the C5a G protein-coupled receptor antagonists in methods for treating OA in an animal in need of such treatment.

The present Action at page 7, bridging page 8 clearly admits that the Specification enables the *in vivo* use of the disclosed compounds to treat OA that is mediated *via* the C5a receptor

utilizing C5a receptor antagonists. The claimed methods have been demonstrated to be effective in *in vivo* animal models of the disease including rodents (see Examples 2 and 5) and canines (see Examples 3, 4, 6, and 7), and this result, *by itself,* is sufficient to enable the claimed methods across their present breadth.

Applicants assert that the requirement of providing a substantial and credible utility for the claimed methods has been met. Applicants need not provide all *possible* utilities to satisfy the "use" requirement, nor need they enable all *possible* utilities of the claimed methods, or demonstrate in vivo that it works across all animal or mammalian species.

Applicants respectfully submit that these assertions of non-enablement by the Examiner are unfounded both in the law, and objectively in consideration of the teaching provided by the specification regarding all aspects of the claimed invention. Therefore, Applicants earnestly request that the enablement rejection against the claimed methods be withdrawn and that the application be placed in condition for immediate allowance.

In attempting to establish a *prima facie* case to support the § 112 rejection of the pending method cell claims, the Action appears to doubt whether the claimed methods are sufficiently enabled to allow those of ordinary skill in the art to practice the treatment of OA on humans. This rejection under § 112, as applied against the claimed methods is misplaced and incorrect. It has long been established that composition claims are enabled by defining any practical use of the claimed compound. *In re Nelson*, 126 USPQ 242 (C.C.P.A. 1960); *Cross v. Iizuka*, 224 USPQ 739 (Fed. Cir. 1995). The specification need not provide exhaustive clinical data (either on animals or humans) to enable how to make and use the claimed invention.

Similarly, in light of the successful *in vivo* animal data as detailed in the various Examples discussed in the specification (and acknowledged by the Examiner on pages 8 and 10

of the Action), the enablement rejection as applied against the pending method claims is unfounded. With respect to the claimed methods, the Office has not provided evidence showing that one of ordinary skill in the art would reasonably doubt the direction and guidance provided in the specification concerning the uses of the disclosed C5a G protein-coupled antagonists in the claimed methods, or that the *in vivo* canine and/or rodent animal model data presented in Examples 2 through 7 would not be predictive of *in vivo* results in other mammals, including, for example, humans. Simply stated, a sufficient *prima facie* case evidencing a legal deficiency in the guidance provided by a fair reading of the specification and claims as a whole by one of ordinary skill in these arts has not been established, and the burden has not been properly shifted to the Applicants to provide rebuttal evidence. Applicants believe this is impermissible under the present Statutes.

Moreover, the Action also appears to be requiring the presence of additional "working" examples demonstrating the clinical effectiveness either in *humans* or in an (unspecified) number of *other animals* in order to "prove" efficacy of the claimed methods. The Action appears to overlook the rodent and canine animal model data included in the application's objective teachings, and instead to fault the Specification for failing to provide clinical results in humans. Clearly, this is an improper standard that is not supported by the governing case law.

In fact, rather than requiring the presence of a working example demonstrating clinical effectiveness for each species within a claimed invention, as apparently required by the instant Action, it is well established that the specification does not even have to include any working examples. M. P. E. P. §2165.01 states this with particular clarity:

> There is no statutory requirement for the disclosure of a specific example. A patent specification is not intended nor required to be a production specification. *In re Gay*, 309 F.2d 768, 135 USPQ 311 (C.C.P.A. 1962).

All that is required to comply with § 112, first paragraph, is for the specification to teach how to make and use the claimed invention so that it may be practiced without *undue* experimentation. In assessing the question of whether "undue" experimentation would be required in order to practice the claimed invention, the relevant term is "undue," and not "experimentation." *In re Angstadt and Griffin*, 190 USPQ 214 (C.C.P.A. 1976).

The Courts have held that the need for *some* experimentation does not render the claimed invention unpatentable under 35 U.S.C. § 112, first paragraph. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ 2d 1016 (Fed. Cir. 1991). As a matter of law, it is also well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

A fair reading of the present specification as a whole provides the requisite teaching on how to utilize the disclosed C5a G protein-coupled receptor antagonist cyclic peptide/peptidomimetic compounds in methods for treating OA in animals. The Specification also demonstrates a credible and substantial utility for the disclosed C5a receptor antagonist cyclic peptides and peptidomimetics both *in vitro*, and *in vivo* in acceptable canine and rodent animal models of OA. Applicants assert that this is sufficient to enable the claimed invention, and as such, respectfully requests that the rejection be withdrawn.

2.7 THE REJECTION OF CLAIMS UNDER 35 U. S. C. § 102(B) IS OVERCOME

Claims 1-2 and 6-20 were rejected as being anticipated by Woodruff* et al. *(Arth. & Rheum., Published online Sept. 27, 2002, 46:2476-2485; hereinafter "Woodruff") "as evidenced by Fairlie"* (WO 99/00406*; hereinafter "Fairlie").

Applicants respectfully traverse.

First, Applicants are puzzled by the citation of a primary reference (Woodruff) "as evidenced by" a secondary reference (Fairlie). Such language seems to suggest that the references were considered together to form the basis of an anticipation rejection. It is well established, however, that a rejection on the grounds of anticipation requires the disclosure, in a single reference, of every element of a claimed invention and requires that each and every facet of the claimed invention be identified in the applied reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051 (Fed. Cir. 1987); *Ex parte Levy*, 17 USPQ2d 1461 (B.P.A.I. 1990).

Since a single reference must teach each and every aspect of the invention in order to anticipate a claim, the fact that the Office has cited Woodruff "as evidenced by Fairlie" does not appear to be a *bona fide* rejection under § 102.

However, if it was the Office's intent to rely solely on the reference by Woodruff, this rejection is also improper; Woodruff *does not teach* each and every element of the claimed methods, namely use of a class of C5a G protein-coupled receptor antagonist cyclic peptide and peptidomimetic compounds in the treatment of OA in an animal. Thus, even if the rejection were taken to mean the Woodruff reference alone was used as a basis for the rejection, this, too, is improper, and thus not citable under § 102 against the pending claims, since Woodruff alone fails to teach each and every element of the claimed invention.

Woodruff discloses that the inhibition of the action of C5a by the C5a antagonist AcF-[ORdChaWR] in a rat model significantly reduced the joint pathology associated with rheumatoid arthritis (RA) in comparison to the nonsteroidal anti-inflammatory drug (NSAID), ibuprofen. Woodruff also discloses that RA is an immune complex disease involving the local

activation of inflammatory cells, predominantly in the smaller peripheral joints and that the factor C5a has long been identified as a likely contributor to the pathogenesis of RA.

These authors conclude from their study that C5a antagonists could have broader therapeutic benefits than NSAIDs as antiarthritic agents for RA. However, the reference by itself does not anticipate each and every element of the claimed invention.

Alternatively, if it was the Office's intent to rely solely on the reference by Fairlie, this rejection is *also* improper under § 102, as Fairlie also does not teach each and every element of the claimed invention, namely use of a class of C5a G protein-coupled receptor antagonist cyclic peptide/peptidomimetic compounds in the treatment of OA in an animal. Thus, the reference by Fairlie is *also* not citable *as a single reference* for the purpose of anticipating the pending claims under § 102.

Applicants note that while Fairlie discloses that C5a is implicated in the pathogenesis of immunoinflammatory conditions such as RA (which displays elevated concentrations of C5a in synovial fluid and plasma) the compounds were assayed for their anti-inflammatory activity, and not for their anti-osteoarthritic activity.

On the basis that each reference must be considered when entering a rejection under section 102, these rejections are improper. Applicants respectfully request that they be withdrawn.

Should the intent of the Examiner have been to cite the combined teachings of the two references (*i.e.,* Woodruff "in view of" Fairlie, or Woodruff "taken together with" Fairlie) in this section of the Action really (permissible only under Section 103 of the Statutes), Applicants preemptively note for the record that the combination of the two references would also neither have taught nor rendered obvious the claimed methods.

To support their position, Applicants respectfully point out, however, that RA and OA are completely different diseases, and that the skilled artisan would have no reason to believe that the compounds disclosed in either Woodruff or Fairlie for treating RA would be of any use in the treatment of OA, a separate disease. To illustrate the complexities of the pathologies of RA and OA, Applicants have provided copies of three references (attached hereto as **Exhibit 1**) which demonstrate that RA and OA are distinctly different disorders, have distinctly different causes, and respond quite differently to conventional treatment modalities:

(1) Neumann *et al., Arth & Rheum.*, **46(4)**:934-945 (April 2002).

(2) Uchida *et al., J. Proteome Res.*, **1**:495-499 (2002)

(3) Excerpt from the Oxford Textbook of Medicine, third edition, vol. 3, 1996. Oxford University Press, Section 18.4, *Rheumatoid Arthritis*, B.P. Wordsworth (pp. 2953-2964) and Section 18.6 *Osteoarthritis*, C. W. Hutton (pp. 2975-2983).

While Applicants agree that the method of the present invention involves the use of compounds disclosed in Fairlie, the finding that these compounds are useful in the treat of OA is a completely surprising and unexpected discovery. The fact that some of the compounds disclosed in Fairlie can be used to treat RA is irrelevant to whether these compounds can be used to treat OA due to the very different and complex mechanisms of the individual diseases.

To that end, Applicants respectfully submit that neither Woodruff or Fairlie teaches a method of treatment of OA that comprises the step of administering an effective amount of an inhibitor of a C5a G protein-coupled receptor to a subject in need of such treatment, in which the inhibitor is a compound which (a) is an antagonist of a C5a G protein-coupled receptor, (b) has substantially no agonist activity, and (c) is a cyclic peptide or peptidomimetic compound of formula-I as disclosed herein.

Applicants respectfully request, therefore, that the rejection be withdrawn, and that no subsequent rejection be entered under Section 103 of the Statutes combining these two references for the purpose of rejecting the pending claims as being legally obvious. If however, the Office believes that such a rejection is tenable, Applicants note for the record that such a rejection would be proper only in a subsequent and ***non-final*** Action.

2.8 REQUEST FOR EXAMINER INTERVIEW

Pursuant to M. P. E. P. § 713.01 and 37 C. F. R. § 1.133, Applicants hereby request an interview between the Examiner and their undersigned representative in order to facilitate an expeditious conclusion of prosecution on the merits in the present application, and to permit expedited allowance and issuance of the pending claims prior to the issuance of any subsequent action on the merits.

Should any issues remain in the mind of the Examiner, or should any claims remain rejected for any reason following entry of the present amendment and consideration of the remarks and response herein, Applicants respectfully request that pursuant to M. P. E. P. §§ 408 and 713.09, the Examiner contact the undersigned representative to arrange a telephonic Examiner Interview at a mutually convenient time to discuss favorable disposition of the case and the resolution of any remaining issues of record ***before the issuance of any subsequent Action on the Merits***. Applicants appreciate in advance the Examiner's willingness to arrange such an interview, should any issues concerning patentability of the pending claims remain following entry of the present amendment and consideration of the Amendment and Response submitted herewith.

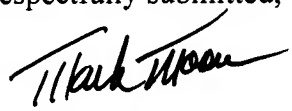
2.9 CONCLUSION

It is respectfully submitted that the pending claims are fully enabled by the Specification, that all pending claims are definite, and free of the cited prior art. Applicants believe that the claims are acceptable under all sections of the Statutes and are now in conditions for ready allowance. Applicants respectfully request the withdrawal of all rejections of record.

Applicants also note for the record their explicit right to re-file claims to one or more aspects of the invention as originally claimed in one or more continuing application(s) retaining the priority claim from the present and parent cases.

Should the Examiner have any questions, a telephone call to the undersigned Applicants' representative would be appreciated.

Respectfully submitted,



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